SUPPORT FOR THE AMENDMENT

The specification has been amended in order to correct obvious typographical errors. Support for the amendment to the claims is found in the original claims. Claims 36-42 are new. Support for the newly added claims is found in the original claims. No new matter is believed to be introduced by the above amendment.

REMARKS

Claims 1-42 are pending. Favorable reconsideration is respectfully requested.

At the outset, Applicants thank Examiner Lukton for the kind and courteous discussion of the present application held on August 6, 2002. Further, Applicants thank Examiner Lukton for his suggestions in overcoming the rejections of the outstanding Office Action, and for indicating that the above amendment when combined with the following remarks would further favorable prosecution.

The Examiner has indicated that Applicants' election is not fully responsive to the Election of Species Requirement. As discussed with Examiner Lukton on August 6, 2002, Applicants elect a member of the ramoplanin family that corresponds to A_2. In accordance with the Examiner's requirement, Applicants have now elected a single species, and therefore the Examiner is reminded to search the prior art based on the chemical formula elected. Further, the Examiner is reminded that once the Examiner has exhausted his search and found that the elected species is allowable, the Examiner must expand his search to include other species of ramoplanin that are presently claimed.

The rejection of Claim 1 under 35 U.S.C. § 103 over Ciabatti in view of Kurihara or

Sekine or Ishida is traversed. Claims 1-42 are neither disclosed nor described by any of the above-mentioned references.

Ciabatti discloses that ramoplanin can be formulated into a gel, a liquid solution for injection, a creme or a suspension. The ramoplanin disclosed by Ciabatti contains an R group, but R' is hydrogen (see page 2, lines 1-48). The Examiner recognizes that Ciabatti fails to suggest that ramoplanin can be formulated into an emulsion.

Kurihara, Sekine and Ishida disclose that cyclosporin and/or specific peptides may be formulated in an emulsion to enhance bioavailability. The Examiner notes that neither cyclosporin nor the specific peptides disclosed in Kurihara, Sekine, or Ishida are ramoplanin.

Applicants traverse the above rejection on the basis that there is motivation to combine Ciabatti with Kurihara, Sekine, and/or Ishida. It is admitted at page 4 of the Official Action that none of the recited references disclose Applicants' claimed formula. Yet, a rejection has been made. The apparent basis for this rejection is "it would have been obvious to one of ordinary skill to formulate ramoplanin into an emulsion." Clearly, the rejection is unsustainable as it fails to present a *prima facie* case.

It has been both recognized and admitted by the Examiner that the applied references lack the requirements, or limitations, set forth in the pending claims. In fact, review of the applied references show that there is absolutely no discussion of disclosure of the chemical compound of formula I in Claim 1, much less the combination of this compound in an emulsion. Given this complete and utter lack of any information pertinent to the claims, Applicants cannot see how one of ordinary skill in the art would perceive, even from a general description, of ramoplanin generally, cyclosporin, or peptide, and wind up at the presently claimed formulation including the specific chemical formula of amended Claim 1. How would one of ordinary skill in the art arrive at the claimed formulation?

The assertion in the Official Action that "it would have been obvious to one of ordinary skill to formulate ramoplanin into an emulsion " puts the cart before the horse - there is no *prima facie* case, especially in light of the fact that Applicants' formula of amended Claim 1 is disclosed in none of the cited references. In order to make such a showing, the Office must present evidence to support its case. However, the Office has presently failed to do so in the Official Action. After the Office provides a *prima facie* case, then the Applicants have the opportunity to rebut the rejection. However, we are not presently at that point. Applicants need not rebut the rejection when the Office has not shown the invention to be at least arguably obvious as contemplated in 35 U.S.C. § 103. In this regard, Applicants note MPEP § 2144.03 regarding reliance on common knowledge or so-called "well-known" prior art. The MPEP instructs that a rejection based upon facts appearing as a result of official notice or emanating from within the personal knowledge of the Examiner must be supported by the Examiner, either in the form of a reference or an affidavit. Applicants here present the seasonable challenge noted in the MPEP to the "facts" taken notice of or assumed in making the obviousness rejection herein, and object because the "facts" taken notice of are so completely non-specific and so completely lack any identification, as to prevent their clear identification and rebuttal.

Accordingly, Applicants submit that the present outstanding rejection is so general in nature, and so lacking in specifics, that it fails to present a supportable *prima facie* case against the pending claims. There has been no attempt to address the several specific limitations pending in each of Applicants' claims. Rather, a general hand waving argument based upon an extremely broad, unsupported premise is the basis for the rejection. This is clearly improper and unsupportable, and the Examiner's attention is respectfully directed to MPEP § 2143 (basic requirements of a *prima facie* case of obviousness). In this section of

the MPEP it is pointed out that three basic criteria must be met: suggestion or motivation to modify to combine reference's teachings; reasonable expectation of success; and a teaching or suggestion of all the claim limitations. In the present case, none of these three criteria have been provided, and Applicants have seasonably challenged any "facts" noticed by the Examiner. In fact, the only "facts" that the Examiner has noticed is the "fact" that the primary reference does not suggest an emulsion and none of the secondary references mention ramoplanin.

In the case that a *prima facie* case is maintained by the Examiner, Applicants respectfully traverse on the grounds that none of the references cited by the Examiner disclose or suggest Applicants' claimed ramoplanin family members. More specifically, these family members include A_1, A_2, A_3, A_1', A_2', A_3'. Of all the references cited by the Examiner, the Examiner admits that none of the secondary references even mention ramoplanin. Further, Ciabatti discloses a ramoplanin, however, R' in the ramoplanin according to Ciabatti is hydrogen. In direct contrast, the present application relates to a pharamaceutical formulation containing family members of ramoplanin having R' that is 2-O-alpha-D-mno-pyranosyl-alpha-D-mannopyranosyl or alpha-D-mannopyranosyl. Therefore, Ciabatti fails to disclose the claimed ramoplanin members, and none of the secondary references disclose or suggest ramoplanin whatsoever. Therefore, the secondary references fail to provide what Ciabatti lacks. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 1-5, 9-18, and 20-35 under 35 U.S.C. § 112, second paragraph, is believed to be obviated by the amendment above. Claim 7 has been amended in order to spell out the abbreviation "q.s.". Claim 14 has been amended in order to recite

"microorganisms whose proliferation is inhibited, reduced, alleviated, or arrested in the presence of ramoplanin". Claim 15 has been amended in order to remove the term "serious".

The Examiner appears to be confused by the phrase "fat emulsion product" recited in Claim 1. The Examiner's attention is directed to page 5, line 25, to page 6, line 7, where Applicants have provided a detailed definition of this phrase. Accordingly, this phrase is not indefinite.

In light of the above, Applicants respectfully request withdrawal of this rejection.

In addition, Applicants have provided an Abstract in accordance with the Examiner's suggestion.

Applicants respectfully submit that the present application is now in condition for allowance. Should anything further be required to place this application in condition for allowance, the Examiner is requested to contact Applicants' attorney by telephone.

Respectfully submitted,

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IN THE SPECIFICATION

Please replace the paragraph on page 1, lines 18-26 with the following:

Ramoplanin factors A'_1, A'_2 and A'_3 have been described in EP-B-318680, the aglycones of any of the above factors have been described in US 5,491,128 while the [tetra hydrogenated] tetrahydrogenated derivatives of any of the above factors have been described in US 5,108,988. A method for selectively increasing the ratio of single major components A_2 and A_3 is described in EP 0259780. All the above mentioned patents are incorporated herein by reference.

Please replace the paragraph from page 1, line 28 through page 2, line 2, with the following:

The structure of ramoplanin and its factors and derivatives have been described in several articles and publications, see R. Ciabatti et al., J. Antib. 1989, 254-267, J. K. Kettenring et al., J. [Antiob.] Antob 1989, 268-275, R. Ciabatti and B. Cavalleri, Bioactive Metabolites from Microorganisms, Elsevier Science [Publisher] Publishers, 1989, 205-219 and M. Kurz and W. Guba, Biochemistry 1996, 35, 12570-12575.

Please replace the paragraph at page 3, lines 9-10 as follows:

R' represents alpha-D-mannopyranosyl or s-o-alpha-D-mannopyranosyl-alpha-D-[mannopyranosil]mannopyranosyl,

Please replace the paragraph at page 6, lines 15-24 as follows:

Typically, a fat emulsion product suitable for preparing a formulation of the invention

comprises an oil phase (usually 2-40%, preferably, 5-25% weight/vol), preferably consisting of vegetable oils such as soybean oil, safflower oil and cottonseed oil, emulsifiers (usually 0.2-5%, preferably, 0.5-2% weight/vol), preferably based on phospholipids of egg source such [as,] as egg lecithin or soybean lecithin, and additives as osmotic agents such as glycerol, sorbitol and xylitol.

Please replace the paragraph from page 6, line 26 through page 7, line 2 as follows:

These fat emulsion products, as commercially available, are emulsions comprising the above mentioned oil phase, emulsifiers and additives dispersed in water for injection and the oil phase is generally present in the emulsion in a percentage (weight/vol) of 5 to 25%. For preparing the i.v. administrable formulation of this invention, the fat [emulsions] emulsion product may be used as such or diluted with saline or water for injection added with an osmotic agent (e.g. glucose) to decrease the oil phase concentration to a lower value and, at the same time, maintaining the desired osmolarity.

Please replace the paragraph on page 7, lines 8-15 as follows:

For instance, with ramoplanin concentrations of about 10 mg/ml, the percentage of the oil phase in the i.v. formulations of the invention may range between 4 to 40% (weight/vol) although are preferred those i.v. fat emulsions wherein the oil phase is between 4 and 25%, and, more preferably, between 8 and 18%, with the range [8-10%being] 8-10% being currently the most preferred concentration.

Please replace the paragraph at page 11, lines 27-33 as follows:

The results of a first set of tolerability studies [in] of representative examples of formulations of the invention in rats at a concentration of ramoplanin of 10 mg/ml (dose 20 mg/kg, administration volume 2 ml/kg), in comparison with a conventional i.v. formulation of the same active principle, are summarized in the following.

Please replace the paragraph on page 12, lines 1-18 as follows:

More particularly, ramoplanin in a conventional [acqueous] aqueous vehicle (0.9% saline) or in the formulations of the invention wherein the proportion of the oil phase in the total formulation is between 2 and 8% (weight/vol) is administered to rats (3-5 animal/group) at a dose of 20 mg/kg (drug concentration 10 mg/ml). The administered volume is 2 ml/kg, according to the animal weight on the day of administration, and the injection speed is 0.1 ml/sec. The intravenous administration is into the caudal vein. Treatments are planned for three days at 24 hours intervals. Control rats receive either [0,9%] 0.9% saline or an equivalent volume of Intralipid® 10%. Behavior and physical appearance are observed frequently the day of dosing. Urine appearance is also recording within 3 h after each daily treatment. Rats are sacrificed 24 h after the last treatment. The results of these experiments are summarized in Table II.

On page 13, please replace the caption for Table II to read as follows:

Table II. Urine appearance, gross pathology at the injection site and clinical observations of rats treated with ramoplanin formulated with Intralipid® or in a conventional [acqueous] aqueous vehicle (0.9% saline)

Please replace the paragraph on page 14, lines 20-33 as follows:

A second set of experiments was carried out to determine tolerability of the formulation of the invention according to the same procedure described above but administering a dose corresponding to 10 mg/kg instead of 20 mg/kg to several groups of three rats for 3 days at 24 hours intervals [with]. The concentration of ramoplanin in the formulation was 1 mg/ml instead of 10 mg/ml and the volume of the formulation administered to each rat was 10 ml/kg instead of 2 ml/kg. The Intralipid® fat emulsion product was added in several different proportion as represented in the following Table III

where the same parameters considered in Table II are reported. The rats were killed 24 h after the last treatment.

On page 15, please replace the caption of Table III to read as follows:

Table III. Urine appearance, gross pathology at the injection site and clinical observations of rats treated with ramoplanin formulated with Intralipid® or in a conventional [acqueous] aqueous vehicle (0.9% saline)

Please replace the paragraph on page 17, lines 12-16 as follows:

When the gentamicin or vancomycin are employed as comparators, they are administered subcutaneously and [the] second shot is given 5 h after infection. Rifampicin and teicoplanin are administered subcutaneously in single dose 10 min after infection.

Please replace the paragraph on page 24, lines 5-8 as follows:

A solution of ramoplanin at 10 mg/ml of activity was prepared in NaCl 0.9% (w/vol). The solution was sterilized by filtration with 0.22 μm pore-size filters.

IN THE CLAIMS

Please amend the claims as follows.

--7. (Twice Amended) A formulation according to claim 1 wherein the fat emulsion product employed for the preparation of said formulation comprises a composition selected from those reported in the following tables:

	Fat emulsion product 1	Fat emulsion product 2	Fat emulsion product 3
Soybean oil (w/vol)	10%	20%	5%
Safflower oil (w/vol)	--	--	5%
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%

Glycerol (w/vol)	2.25%	2.25%	2.5%
Fatty acids composition of vegetable oils (w/vol)			
Linoleic acid	50%	50%	65.8%
Oleic acid	26%	26%	17.7%
Palmitic acid	10%	10%	8.8%
Linolenic acid	9%	9%	4.2%
Stearic acid	3.5%	3.5%	3.4%
Osmolarity (mOsm/L)	260	268	276
Approximate pH	8	8	8
Fat particle size (μm)	0.5	0.5	0.4
Caloric value (cal/ml)	1.1	2.0	1.1
Size (ml)	50, 100	50, 100	25, 50
	250 or	250 or	100, 200
	500	500	Or 500
	Fat emulsion product 4	Fat emulsion product 5	Fat emulsion product 6
Soybean oil (w/vol)	10%	10%	20%
Safflower oil (w/vol)	10%	--	--
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%
Glycerol (w/vol)	2.5%	2.5%	2.5%
Fatty acids composition of vegetable oil (w/vol)			
Linoleic acid	65.8%	54.5%	54.5%
Oleic acid	17.7%	22.4%	22.4%
Palmitic acid	8.8%	10.5%	10.5%
Linolenic acid	4.2%	8.3%	8.3%
Stearic acid	3.4%	4.2%	4.2%
Osmolarity (mOsm/L)	258	284	292

Approximate pH	8.3	8.3	8.3
Fat particle size (μm)	0.4	0.4	0.4
Caloric value (cal/ml)	2.0	1.1	2.0
Size (ml)	25, 50	100, 200	200 or
	200 or	Or 500	550
	500		

and water for injection is from quite small [q.s]. to 100%.

14. (Twice Amended) A formulation according to claim 1 for treatment of infections caused by [agents that are susceptible to] microorganisms whose proliferation is inhibited, reduced, alleviated, or arrested in the presence of ramoplanin or an antibiotic of the ramoplanin family.

15. (Twice Amended) A method of treating Gram positive infections, comprising administering the formulation according to claim 1 to a patient in need thereof [for the treatment of Gram positive infections - such as bacteremia, endocarditis or pneumonia].

--Claims 36-42 are new.--